Commentary

Is the ability of stool DNA test enough for practical use in colorectal cancer screening?

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Deaths from colorectal cancer (CRC) can be reduced considerably by implementing an adequate screening. Moreover, CRC screening has another merit that can detect CRC in an early stage, and can also detect precancerous lesions, resulting in the decrease in the medical cost involved in the treatment of CRC. Hence, CRC screening has been prevalent in many countries (1), and in particular, the outstanding reduction in the death from CRC in the United States is considered largely attributable to the increase in the rate of CRC screening.

As one of the screening methods of CRC, the majority of countries adopted a fecal occult blood test, which has been recently called as a fecal immunochemical test (FIT), because hemoglobin concentrations in stools are measured with an immunochemical method using an antibody specific to human hemoglobin. FITs have advantages of more sensitive and specific nature to human hemoglobin, no diet restriction requirement, and quantitative measurement with an automated analyzer. FITs, therefore, have recently replaced the formerly used guaiac-based test. Both of the two major guidelines in the United States also recommended the stool-based test as one of the CRC screening methods. The U.S. Preventive Task Force (USPTF) guideline recommended FIT, sigmoidoscopy, and colonoscopy, while the guideline of the American Gastroenterological Association suggested a stool DNA test in place of a FIT (2,3). The main reason of the avoidance of recommendation of stool DNA testing by USPTF is the lack of sufficient evidence as to the benefit and cost-effectiveness of the method. In fact, previous reports did not show that the results of a stool DNA test were always superior to those of a FIT (4,5).

The report recently published in the *New England Journal of Medicine* indicated the results of the newly developed stool DNA test used for a prospective cohort consisted of subjects at average risk of CRC (6), in comparison to the results of a FIT. The stool DNA test used in the report was comprised of one genetic marker (*K-ras* mutation), two methylation markers, and an immunochemical assay for human hemoglobin. The results indicated that the stool DNA test was superior in sensitivities for CRC (more than 90%) and advanced neoplasia (more than 40%) to a FIT. Although the results are outstanding and may reveal the new era of the CRC screening, meticulous reading of the paper revealed not only anticipation but also several problems in the methodology.

Undoubtedly, there are advantages in the DNA test based on the results of the paper. First, the DNA test is approximately 20 points more sensitive to significant colorectal neoplasia (CRC and advanced neoplasia) than a FIT. Higher sensitivity reduces false negative cases. The false negative results could easily lead the subjects to fatal status. Hence, achievement of the high sensitivity to colorectal neoplasia by the noninvasive method (without the burden of endoscopy or radiation exposure) using stools is of great value.

Second, the high sensitivities for neoplasia in the proximal colon and sessile serrated polyps are worthy to note. According to the previous reports (7,8), fecal tests including the guaiac-based tests and FITs were less sensitive to neoplasia in the proximal colon than that in the distal colon and the rectum maybe because hemoglobin in stools was diluted and/or degenerated. In this context, the new stool DNA test probably covers those lesions by detecting DNA mutation or methylation. Moreover, the high sensitivity to sessile serrated polyps deserves special

mention. Sessile serrated polyps, which are recently regarded as a precursor lesion of CRC with microsatellite instability, are usually flat-shaped, normally-colored (i.e., less likely to bleed), and located at the proximal colon. Sessile serrated polyps are usually highly methylated tumors and the DNA test probably indentified those lesions by the detection of methylation. Thus, casting spotlight to the outcasts by the current screening methodology is an excellent outcome of the article. It should have been more interesting if which genetic or epigenetic markers had contributed to the detection of such lesions had been shown in the article.

Despite such admirable outcomes, the paper harbors substantial problems. First of all, lower specificities to CRC and advanced neoplaisa should be the focus of criticism. Lower specificity indicates the increase in false positive cases. Increase in the false positive cases would also increase the number of subjects who have to undergo close examinations including colonoscopy. The raised number of the close examinations would enlarge burdens of physicians who would perform colonoscopy. In addition, the increase in close examinations would inevitably increase the medical cost. More importantly, increase in the false positive cases would make subjects become unmotivated to undergo screening tests, and reduce adherence to CRC screening, resulting in the increase in the deaths from CRC.

The lower specificity appears to be caused by the substantial problem of the DNA test, because the test is comprised of the addition of *K-ras* mutation and methylation assays to the hemoglobin immunoassay. As the authors indicated, the isolated performance of the hemoglobin immunoassay component of the multitarget DNA test was similar to that of the FIT. Therefore, both the increase in sensitivity and the decrease in specificity of the test are considered to be mainly attributable to the addition of the *K-ras* test and methylation panel. Moreover, because mutation analysis is not likely to produce false positive cases, large portion of the false positive cases would have been responsible to methylation analysis. Hence, the number and location of methylation detection sites may have room for reconsideration. Meanwhile, the lower specificity of methylation analysis may reflect methylation status of normal mucosa, because normal mucosa of patients who would develop neoplastic lesions is considerably methylated before neoplasia development (9). Therefore, it appears to be interesting to verify whether the false positive patients on the methylation panel of the test would develop colorectal neoplasia in the future.

The next drawback of this study is that the criterion of the test positivity was defined by the unique algorithm in an arbitrary manner. The black box of the arbitrarily defined algorithm must be validated by using different subject cohorts. The quality of the DNA test and the validity of the algorithm must be ascertained by future studies.

The final shortcoming of the DNA test is the high rate of invalid preparations of the material: more than 5%. Due to recent progress in the skill of colonoscopy, the intubation rate of colonoscope into the cecum has become more than 95%, maybe nearly 100%. In this sense, the current method of the collection of DNA from stools may not be sufficient for the DNA testing and the technical innovation in this field is largely anticipated.

The paper was written in complying with the sponsor, the manufacturer of the DNA test. Maybe due to the intension of the sponsor, the paper largely emphasized sensitivity of screening modalities rather than specificity in the discussion. However, what is really needed in screening tests is not sensitivity alone. Specificity and cost-effectiveness are also important factors for practical use of screening. For further verification of the DNA testing for practical use, meticulous cost-effective analysis with disclosure of the cost of the DNA test should be performed. Different from the past, recent progress of the simulation models has enabled the precise evaluation of validity and cost-effectiveness of a certain screening method (10). In the field of CRC, the personal and social costs and burdens involved in close examinations including colonoscopy and treatments including the long-term administration of expensive chemotherapeutic agents are extremely high. Hence, such simulation studies are eagerly required. The ability of other screening modalities including colonoscopy and computed tomographic colonography has also been improved. The DNA test has to compete with those modalities in practical usefulness including validity, safety, cost-effectiveness and accessibility.

The sensitivity of more than 90% achieved by the DNA test appears to be as high as it gets. No more improvement of sensitivity could be achieved without lowering specificity. The putative contributors to the increase in the screening rate of CRC in the United States are improvement of the skill of colonoscopy and political success to motivate subjects to undergo screening. Further increase in the sensitivity of one screening modality would not be of great importance in the anti-CRC strategy in the future. In this sense, it is doubtful that the development of any stool DNA test could practically surpass the screening method of the

combination of annual two-day FITs with colonoscopy of several years interval.

In conclusion, the stool DNA test reported recently has promise as one of the candidates of screening modality of CRC in the future. In particular, higher sensitivity for neoplasia in the proximal colon and sessile serrated polyps is a great advantage. However, the lower specificity and lower successful rate of the preparation of stool DNA that would result in insufficient cost-effectiveness are great obstacles for practical application. For practical use, further improvement of the methodology of the collection of DNA and meticulous analysis of cost-effectiveness in comparison to currently available screening modalities using simulation models are required.

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